

## **ATTACHMENT 1: TECHNOLOGY READINESS LEVEL (TRL) DEFINITIONS**

Introduction: Technology Readiness Levels (TRLs) are a systematic metric/measurement system that supports assessments of the maturity of a particular technology and the consistent comparison of maturity between different types of technology. TRLs were originally developed and used by the National Aeronautics and Space Administration (NASA) for technology planning. The use of TRLs has been widely adopted in government and industry. The Department of Defense (DoD) has adopted the use of TRLs as documented in the current DoD-5000 series publications. The table below provides notional TRL descriptions for both non-medical and medical systems.

<b><u>Technology Readiness Level 1</u></b> <b>Basic principles observed and reported</b>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
Lowest level of technology readiness. Scientific research begins to be translated into applied research and development. Examples might include paper studies of a technology's basic properties.	<b>Review of Scientific Knowledge Base.</b> Active monitoring of scientific knowledge base. Scientific findings are reviewed and assessed as a foundation for characterizing new technologies

<b><u>Technology Readiness Level 2</u></b> <b>Technology concept and/or application formulated</b>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
Invention begins. Once basic principles are observed, practical applications can be invented. Applications are speculative and there may be no proof or detailed analysis to support the assumptions. Examples are limited to analytic studies.	<b>Development of Hypotheses and Experimental Designs.</b> Scientific "paper studies" to generate research ideas, hypothesis, and experimental designs for addressing the related scientific issues. Focus on practical applications based on basic principles observed. Use of computer simulation or other virtual platforms to test hypotheses.

<b><u>Technology Readiness Level 3</u></b> <b>Analytical and experimental critical function and/or characteristic proof of concept</b>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
Active research and development is initiated.	<b>Target/Candidate Identification and</b>

<p>This includes analytical studies and laboratory studies to physically validate analytical predictions of separate elements of the technology. Examples include components that are not yet integrated or representative.</p>	<p><b>Characterization of Preliminary Candidate(s).</b> Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components, and begin characterization of candidate(s). Preliminary efficacy demonstrated in <i>vivo</i>.</p> <p>3A. Identify target and/or candidate.</p> <p>3B. Demonstrate in <i>vitro</i> activity of candidate(s) to counteract the effects of the threat agent.</p> <p>3C. Generate preliminary in <i>vivo</i> proof-of-concept efficacy data (non-GLP).</p>
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<p align="center"><b><u>Technology Readiness Level 4</u></b>  <b>Component and/or breadboard validation<sup>†</sup> in laboratory environment.</b></p>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
<p>Basic technological components are integrated to establish that they will work together. This is relatively “low fidelity” compared to the eventual system. Examples include integration of “ad hoc” hardware in the laboratory.</p>	<p><b>Candidate Optimization and Non-GLP In Vivo Demonstration of Activity and Efficacy.</b> Integration of critical technologies for candidate development. Initiation of animal model development. Non-GLP in <i>vivo</i> toxicity and efficacy demonstration in accordance with the product's intended use. Initiation of experiments to identify markers, correlates of protection, assays, and endpoints for further non-clinical and clinical studies.</p> <p><i>Animal Models:</i> Initiate development of appropriate and relevant animal model(s) for the desired indications.</p> <p><i>Assays:</i> Initiate development of appropriate and relevant assays and associated reagents for the desired indications.</p> <p><i>Manufacturing:</i> Manufacture laboratory-scale (i.e. non-GMP) quantities of bulk product and proposed formulated product.</p> <p>4A Demonstrate non-GLP in <i>vivo</i> activity and potential for efficacy consistent with the</p>

	<p>product's intended use (i.e. dose, schedule, duration, route of administration, and route of threat agent challenge).</p> <p>4B Conduct initial non-GLP toxicity studies and determine armacodynamics and pharmacokinetics and/or immune response in appropriate animal models (as applicable).</p> <p>4C Initiate experiments to determine assays, parameters, surrogate markers, correlates of protection, and endpoints to be used during non-clinical and clinical studies to further evaluate and characterize candidate(s).</p>
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<p align="center"><b><u>Technology Readiness Level 5</u></b>  <b>Component and/or breadboard validation in relevant environment.</b></p>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
<p>Fidelity of breadboard technology increases significantly. The basic technological components are integrated with reasonably realistic supporting elements so it can be tested in a simulated environment. Examples include “high fidelity” laboratory integration of components.</p>	<p><b>Advanced Characterization of Candidate and Initiation of GMP Process Development.</b> Continue non-GLP <i>in vivo</i> studies, and animal model and assay development. Establish draft Target Product Profiles. Develop a scalable and reproducible manufacturing process amenable to GMP.</p> <p><i>Animal Models:</i> Continue development of animal models for efficacy and dose· ranging studies.</p> <p><i>Assays:</i> Initiate development of in· process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate.</p> <p><i>Manufacturing:</i> Initiate process development for small-scale manufacturing amenable to GMP.</p> <p><i>Target Product Profile:</i> Draft preliminary Target Product Profile. Questions of shelf life, storage conditions, and packaging should be considered to ensure that anticipated use of the</p>

	<p>product is consistent with the intended use for which approval will be sought from FDA.</p> <p>5A Demonstrate acceptable Absorption, Distribution, Metabolism and Elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing.</p> <p>5B Continue establishing correlates of protection and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose once clinical data are obtained.</p>
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<p align="center"><b><u>Technology Readiness Level 6</u></b>  <b>System/subsystem model or prototype demonstration in a relevant environment.</b></p>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
<p>Representative model or prototype system, which is well beyond that of TRL 5, is tested in a relevant environment. Represents a major step up in a technology's demonstrated readiness. Examples include testing a prototype in a high-fidelity laboratory environment or in simulated operational environment.</p>	<p><b>GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s).</b> Manufacture GMP pilot lots. Prepare and submit Investigational New Drug (IND) package to FDA and conduct Phase 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article.</p> <p><i>Animal Models:</i> Continue animal model development via toxicology, pharmacology, and immunogenicity studies.</p> <p><i>Assays:</i> Qualify assays for manufacturing quality control and immunogenicity, if applicable.</p> <p><i>Manufacturing:</i> Manufacture, release and conduct stability testing of GMP bulk and formulated product in support of the IND and clinical trial(s).</p> <p><i>Target Product Profile:</i> Update Target Product Profile as appropriate.</p>

	<p>6A Conduct GLP animal studies for toxicology, pharmacology, and immunogenicity as appropriate.</p> <p>6B Prepare and submit full IND package to FDA to support initial clinical trial(s).</p> <p>6C Complete Phase 1 clinical trial(s) that establish an initial safety and pharmacokinetics assessment.</p>
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<p align="center"><b><u>Technology Readiness Level 7</u></b>  <b>System prototype demonstration in an operational environment.</b></p>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
<p>Prototype near, or at, planned operational system. Represents a major step up from TRL 6, requiring demonstration of an actual system prototype in an operational environment such as an aircraft, vehicle, or space. Examples include testing the prototype in a test bed aircraft.</p>	<p><b>Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)<sup>3</sup>.</b>  Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate. Conduct Phase 2 clinical trial(s).</p> <p><i>Animal Models:</i> Refine animal model development in preparation for pivotal GLP animal efficacy studies.</p> <p><i>Assays:</i> Validate assays for manufacturing quality control and immunogenicity if applicable.</p> <p><i>Manufacturing:</i> Scale-up and validate GMP manufacturing process at a scale compatible with USG requirements. Begin stability studies of the GMP product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production.</p> <p><i>Target Product Profile:</i> Update Target Product Profile as appropriate.</p> <p>7A Conduct GLP animal efficacy studies as appropriate for the product at this stage<sup>4</sup>.</p>

	7B Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2) <sup>3</sup> .
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<b><u>Technology Readiness Level 8</u></b> <b>Actual system completed and qualified through test and demonstration.</b>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
Technology has been proven to work in its final form and under expected conditions. In almost all cases, this TRL represents the end of true system development. Examples include developmental test and evaluation of the system in its intended weapon system to determine if it meets design specifications.	<p><b>Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials<sup>3</sup>, and FDA Approval or Licensure.</b> Finalize GMP manufacturing process. Complete pivotal animal efficacy studies or clinical trials (e.g., Phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit NDA/BLA.</p> <p><i>Manufacturing:</i> Complete validation and manufacturing of consistency lots at a scale compatible with USG requirements. Complete stability studies in support of label expiry dating.</p> <p><i>Target Product Profile:</i> Finalize Target Product Profile in preparation for FDA approval.</p> <p>8A Complete final pivotal GLP animal efficacy studies or pivotal clinical trials (e.g., Phase 3), and any additional expanded clinical safety trials as appropriate for the product<sup>3</sup>.</p> <p>8B Prepare and submit New Drug Application (NDA) or Biologics Licensing Application (BLA) to the FDA.</p> <p>8C Obtain FDA approval or licensure.</p>

<b><u>Technology Readiness Level 9</u></b> <b>Actual system proven through successful mission operations.</b>	
<b>Acquisition Guidebook (October 2012)</b>	<b>Medical Description (December 2008)</b>
Actual application of the technology in its final form and under mission conditions, such as	<b>Post-Licensure and Post-Approval Activities.</b> 9A Commence post-licensure/post-

those encountered in operational test and evaluation. Examples include using the system under operational mission conditions.	<p>approval and Phase 4 study commitments, such as safety surveillance, data to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate<sup>5</sup>.</p> <p>9B Maintain manufacturing capability as appropriate.</p>
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<sup>1</sup>This document is designed for evaluating the maturity of medical countermeasure development programs. For a detailed description of development processes for assays and animal models, please consult the Technology Readiness Level for Product Development Tools (PDTs), developed by the PDT Working Group of the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE).

<sup>2</sup>This document does not serve as official FDA guidance. For the purposes of a regulatory application seeking licensure or approval for a specific medical product, additional data may be required by the FDA.

<sup>3</sup> Identification of later regulatory stages of clinical development in this documents (e.g. Phase 2, Phase 3) may not apply to some products being developed under the “Animal Rule.” Other than human safety and pharmacology studies, no additional data may be feasible or ethical to obtain.

<sup>4</sup> These could include GLP animal efficacy studies required by the FDA at this stage in support of the Emergency Use Authorization (EUA). Requirements for issuance of an EUA will be handles on a case-by-case basis and will depend on the nature abd extent of the threat at any point during the product development timeline, from the initiation of Phase 1 studies through licusure or approval. GLP animal efficacy study requirements may also vay by product type (e.g. vaccine, therapeutic, prophylactic) and U.S. Government agency program office.

<sup>5</sup> For products approved under the “Animal Rule,” confirmatory efficacy data is required and may be obtained from use during an event.